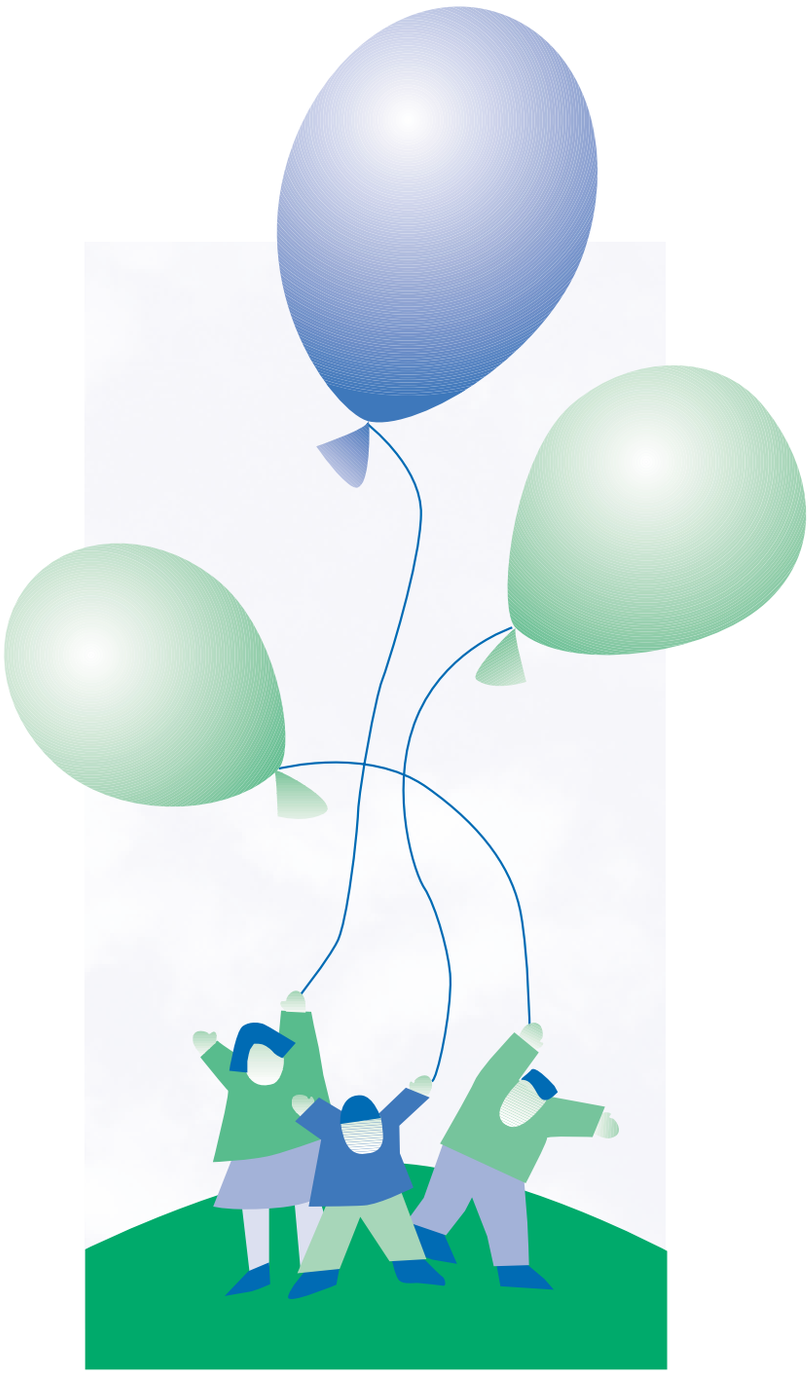
California Environmental Protection Agency,
Office of Environmental Health Hazard Assessment

Children's Environmental Health Symposium



PROGRAM

Children's Environmental Health Symposium

AGENDA

DAY ONE: MONDAY, MAY 1

8:30 a.m. OVERVIEW

Risk Assessment in California and the Need for Further Investigation to Insure Infant and Children Protection
Melanie Marty, Office of Environmental Health Hazard Assessment
Andy Salmon, Office of Environmental Health Hazard Assessment

8:45 a.m. KEYNOTE ADDRESS

Children and the Environment: An Overview of Risks, Rates and Policy Implications
Lynn Goldman, M.D., M.P.H., Johns Hopkins University

9:15 a.m. DEVELOPMENTAL TOXICITY

Mechanisms Underlying Children's Susceptibility to Environmental Toxicants
Elaine Faustman, Ph.D., University of Washington

9:50 a.m. Adolescent Health and the Environment
Mari Golub, Ph.D., Office of Environmental Health Hazard Assessment

10:20 a.m. Panel Discussion
Moderator: Jim Donald, Office of Environmental Health Hazard Assessment
Elaine Faustman, Mari Golub

10:40 a.m. BREAK

11:00 a.m. NEUROTOXICITY

Development and Maturation of the Nervous System: Neurobiological Basis of Vulnerability to Environmental Contaminants
Stanley Barone, Jr., Ph.D., U.S. Environmental Protection Agency

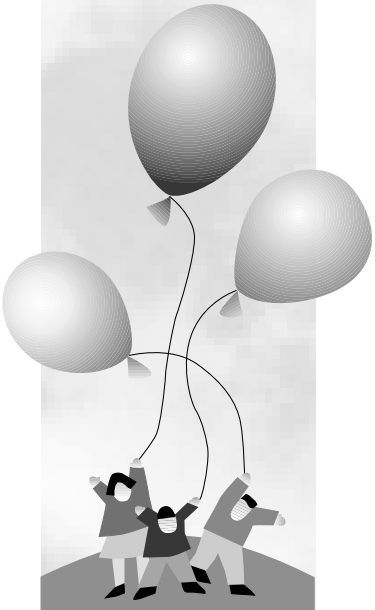
11:30 a.m. Specific Examples of Impacts of Toxicants on the Developing and Maturing Nervous System
Deborah Rice, Ph.D., U.S. Environmental Protection Agency

12:10 p.m. Panel Discussion
Moderator: Mari Golub, Ph.D., Office of Environmental Health Hazard Assessment
Stanley Barone, Jr., Deborah Rice

12:30 p.m. LUNCH BREAK

2:00 p.m. OVERVIEW

Science Strategy for EPA's Office of Children's Health Protection
Michael Firestone, Ph.D., Office of Children's Health Protection, Environmental Protection Agency



AGENDA

DAY ONE: MONDAY, MAY 1 (cont.)

2:15 p.m. **THE LUNG**

Development and Maturation of the Lung: Age Specific Vulnerabilities
Ira Tager, M.D., M.P.H., University of California, Berkeley

2:45 p.m. **Impacts of the Criteria Air Pollutants on the Developing Lung**
John Balmes, M.D., University of California, San Francisco

3:15 p.m. **BREAK**

3:30 p.m. **Possible Role of Hazardous Air Pollutants in Adverse Respiratory Responses Among Children**
George Leikauf, Ph.D., University of Cincinatti Medical Center

4:00 p.m. **Panel Discussion**
Moderator: Melanie Marty, Office of Environmental Health Hazard Assessment
Ira Tager, John Balmes, George Leikauf
Kent Pinkerton, Ph.D., University of California, Davis

4:30 p.m. **ADJOURN**

DAY TWO: TUESDAY, MAY 2

8:30 a.m. **ENDOCRINE FUNCTION**

PCB's, DDT, Breastfeeding, and Growth in North Carolina Children Followed From Birth to Puberty
Walter Rogan, M.D., National Institute of Environmental Health Sciences

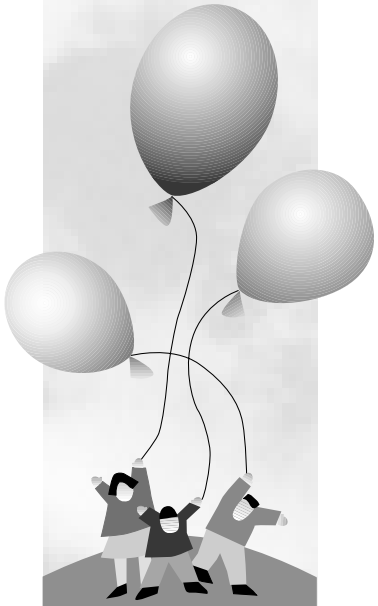
9:00 a.m. **Panel Discussion**
Moderator: Andy Salmon, Office of Environmental Health Hazard Assessment
Walter Rogan
Brenda Eskenazi, Ph.D., M.A., University of California, Berkeley

9:20 a.m. **IMMUNOTOXICITY AND SENSITIZATION**

Development and Maturation of the Immune System: Vulnerability to Toxicants
Steven Holladay, Ph.D., Virginia Polytechnic University

10:00 a.m. **BREAK**

10:20 a.m. **Developmental Immunology and Potential Windows of Vulnerability to Asthma**
John Armstrong, Ph.D., Immuarm, Inc.



AGENDA

DAY TWO: TUESDAY, MAY 2 (cont.)

IMMUNOTOXICITY AND SENSITIZATION (CONT.)

10:40 a.m. **Panel Discussion**
Moderator: Mark Miller, M.D., M.P.H., Office of Environmental Health Hazard Assessment
Steven Holladay, John Armstrong

11:00 a.m. **CARCINOGENICITY**

Re-evaluating Cancer Risk Estimates for Short-term Exposure Scenarios
Chris Portier, Ph.D., National Institute of Environmental Health Sciences

11:30 a.m. **LUNCH BREAK**

1:00 p.m. **Characteristics of Risk of Perinatal Carcinogenesis**
Lucy Anderson, Ph.D., D.A.B.T., National Cancer Institute

1:30 p.m. **Panel Discussion**
Moderator: Lauren Zeise, Office of Environmental Health Hazard Assessment
Chris Portier, Lucy Anderson

2:00 p.m. **PHARMACOKINETIC ISSUES**

Pharmacokinetic Parameters
Dale Hattis, Ph.D., Clark University

2:30 p.m. **BREAK**

2:50 p.m. **Exposure to Dose Models: Their Uses in Helping Access Relevant Dose in Children**
Jerry Blancato, Ph.D., U.S. Environmental Protection Agency

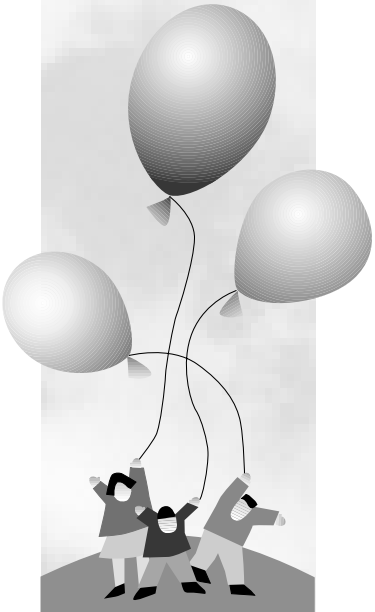
3:20 p.m. **Xenobiotic Metabolism and Chemical Fate from Early Childhood Onward**
Gary Ginsberg, Ph.D., Connecticut Department of Public Health

3:50 p.m. **Panel Discussion**
Moderator: Joe Brown, Office of Environmental Health Hazard Assessment
Dale Hattis, Jerry Blancato, Gary Ginsberg
Delia Dempsey, M.D., University of California, San Francisco

4:20 p.m. **WRAP-UP & BRAINSTORMING**

Where Do We Go From Here?

4:40 p.m. **ADJOURN**



ABSTRACTS

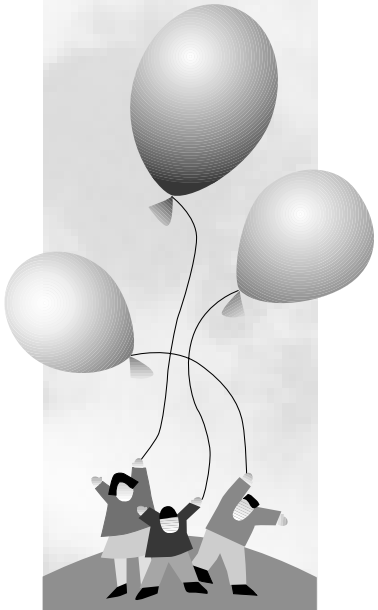
Monday, May 1, 2000
8:45 a.m.

KEYNOTE ADDRESS

Children and the Environment: An Overview of Risks, Rates and Policy Implications

Lynn Goldman, M.D., M.P.H., Johns Hopkins University

Children are not little adults when it comes to health risks of environmental exposures. Children differ from adults in many respects: exposure, metabolism, growth, development, and potential for long-term effects. Children may be more exposed than adults, because they have greater intake of air, water, and food per body weight than adults do. The behaviors of young children, which involve more contact with the floor and more hand-to-mouth activity, result in greater exposure to contaminants in house dust or soil. Metabolism of pollutants through hepatic and renal pathways changes rapidly from birth through the first few years of life. Therefore, at various stages of development, children may be more or less capable of breaking down, excreting, inactivating, or activating toxic substances. Because children are rapidly growing and developing, there are "windows of vulnerability" for effects on organ systems from gestation through adolescence. Finally, because children have a long life expectancy, effects with long latency have a longer time to manifest themselves. Recently, federal environmental health and safety policies have evolved toward stronger protection of children. The USEPA established an office of Children's Health Protection and policies requiring that children's risks be taken into account in decisions. Congress enacted the Food Quality Protection Act and Safe Drinking Water Act in 1996, both of which contain child-protective provisions. Under a presidential Executive Order on Children's Environmental Health and Safety, task forces are moving forward with new efforts to prevent lead poisoning, cancer, disabilities, asthma, and injuries.



ABSTRACTS

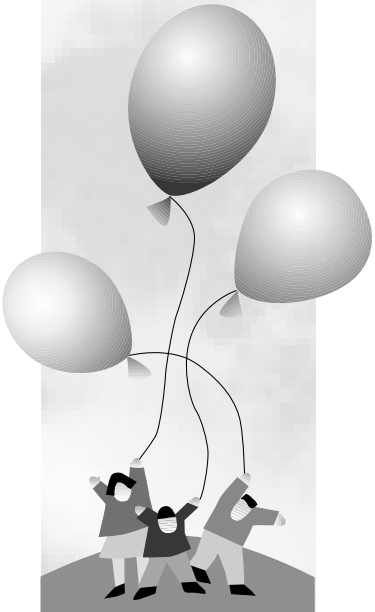
Monday, May 1, 2000
9:15 a.m.

DEVELOPMENTAL TOXICITY

Mechanisms Underlying Children's Susceptibility to Environmental Toxicants

Elaine Faustman, Ph.D., University of Washington

ABSTRACT UNAVAILABLE



ABSTRACTS

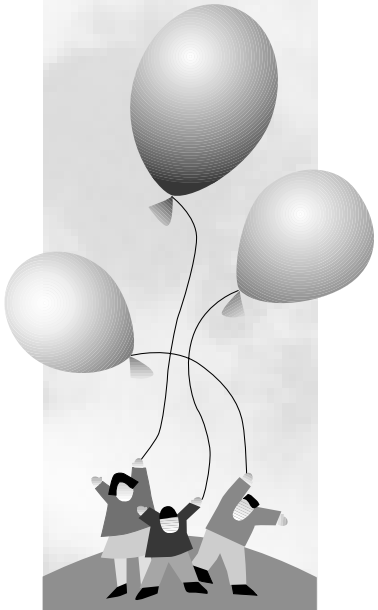
Monday, May 1, 2000
9:50 a.m.

DEVELOPMENTAL TOXICITY

Adolescent Health and the Environment

Mari Golub, Ph.D., Office of Environmental Health Hazard Assessment

Although there is no coherent body of literature in this area, there are a number of reasons why adolescents can be considered particularly sensitive to environmental toxicants. The biology of adolescence is distinctive and provides opportunities for unique actions of toxicants. Both disruption of maturational processes and disruption of functions critical to this period of the life span can occur. The maturing reproductive, skeletal, immune, and central nervous systems could be permanently affected by toxicants that target them, perhaps contributing to later occurrence of infertility, autoimmune disease, and psychopathology. Adolescence is a period of increased risk taking and intellectual competition, making effects on the nervous system particularly debilitating. Exposures also change in adolescence due to introduction to the workplace and recreational drugs. Rapid growth and sex-dependent changes in morphology and metabolism contribute to altered response to toxicants. Basic research needs to use appropriate experimental designs and animal models to study adolescent toxicology, and risk assessment needs to take into account pharmacokinetic and lifestyle factors, in order to protect children during their final stages of maturation.



ABSTRACTS

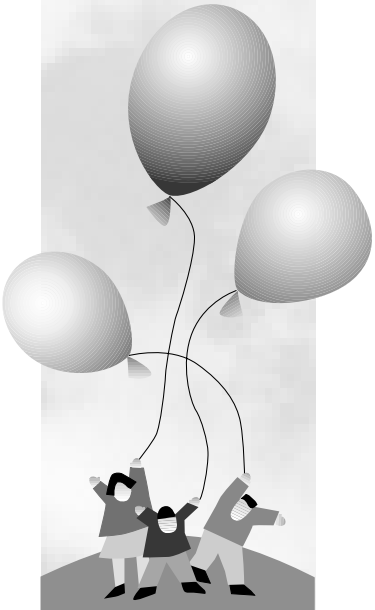
Monday, May 1, 2000
11:00 a.m.

NEUROTOXICITY

Development and Maturation of the Nervous System: Neurobiological Basis of Vulnerability to Environmental Contaminants

Stanley Barone, Jr., Ph.D., U.S. Environmental Protection Agency

The susceptibility of the developing nervous system to damage following exposure to environmental contaminants is believed to be based upon the critical nature of the organizational events that occur in both a regionally and temporally-dependent manner. The age-related susceptibility of the nervous system is based upon the protracted time over which the nervous system develops. This temporal vulnerability spans the embryonic, fetal, infant and adolescent periods. These organizational events are determined by the rate and duration of critical developmental processes like proliferation, migration, differentiation, synaptogenesis, myelination and apoptosis. Normal development of the nervous system requires the coordinated ontogeny of all of these processes. Previously, adverse effects of prototypical developmental neurotoxicants have been shown to be mediated by effects on these developmental processes. Perturbations of these processes during development can result in long-term persistent consequences that affect the structure and function of the nervous system and could account for qualitative differences in age-related susceptibility of the developing nervous system as compared to the adult nervous system. The presentation will focus on the description of the ontogeny of these processes and a brief comparison of ontogeny in animal models and humans during development. Examples of perturbations of these processes and their outcomes will also be used to illustrate the developmental vulnerability of the nervous system. A discussion of developmental milestones and the relevance of transient effects on developmental endpoints will be presented. In addition, the discussion will include consideration of how alterations in these processes may relate to toxicity through numerous mechanisms that may affect convergence of these developmental processes on possible final common pathways leading to altered neural development such as altered neuron number, differentiation, and/or altered connectivity. Thus, utilization of mechanistically-based constructs that includes these developmental processes may improve the detection and reduce uncertainty about the adverse nature of effects following developmental exposure to environmental neurotoxicants. (This abstract does not necessarily reflect USEPA policy.)



ABSTRACTS

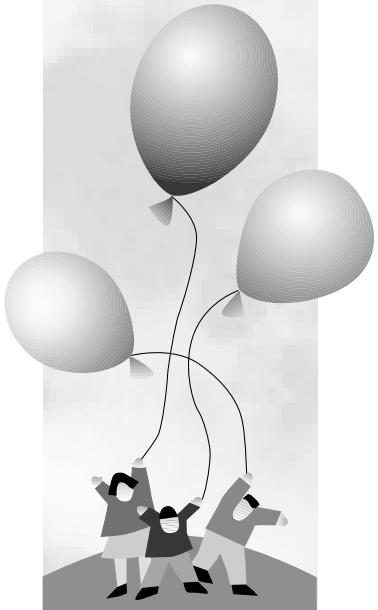
Monday, May 1, 2000
11:30 a.m.

NEUROTOXICITY

Specific Examples of Impacts of Toxicants on the Developing and Maturing Nervous System

Deborah Rice, Ph.D., U.S. Environmental Protection Agency

ABSTRACT UNAVAILABLE



ABSTRACTS

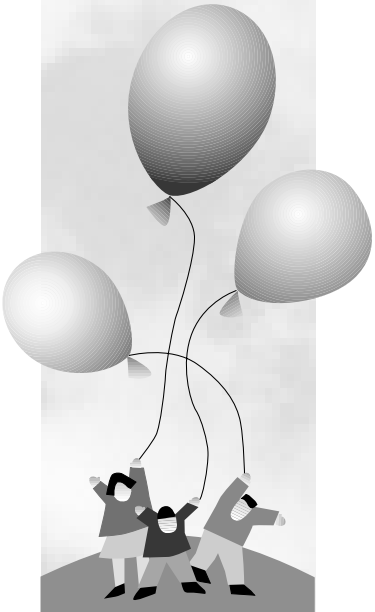
Monday, May 1, 2000
2:00 p.m.

OVERVIEW

Science Strategy for EPA's Office of Children's Health Protection

Michael Firestone, Ph.D., Office of Children's Health Protection,
Environmental Protection Agency

The purpose of this presentation is to provide information regarding the role of EPA's Office of Children's Health Protection and its science team toward improving the scientific basis necessary to protect children from environmental hazards. The presentation will focus on current and possible future activities related to risk assessment guidance, testing guidelines/protocols, science policy and information sharing.



ABSTRACTS

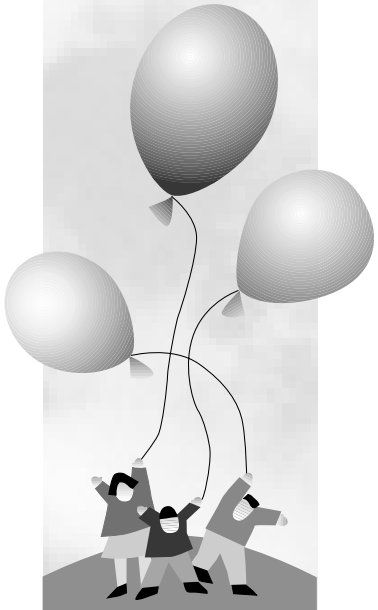
Monday, May 1, 2000
2:15 p.m.

THE LUNG

Development and Maturation of the Lung: Age Specific Vulnerabilities

Ira Tager, M.D., M.P.H., University of California, Berkeley

A considerable body of epidemiological data has been developed which indicate that exposure to environmental agents early in life, which includes the prenatal period, may have consequences for respiratory health in children. It is well known that passive exposure to tobacco smoke has effects on respiratory function which can be observed as early as the first few days after birth. These lowered levels of lung function appear to be markers for an increased risk of wheezing respiratory illness early in life, airways reactivity in childhood and into adult life and disease severity (asthma). Some data indicate that environmental tobacco smoke exposure may be a causal risk factor for asthma and certainly contributes to increased morbidity of asthma in childhood. More recent data indicate that exposure to ambient air pollutants can result in an increased risk of low birth weight, premature labor, intra-uterine growth retardation and decreased lung function and increased respiratory morbidity in childhood and into adult life. There also is evidence that low birth weight infants might be at greater risk for adverse respiratory responses to ambient air pollution. This presentation will review the basic elements of the development of the respiratory system in the fetus and early childhood. The presentation will relate this development to the potential points of vulnerability which increases children's risk of respiratory morbidity and may provide explanations for the epidemiological findings noted above.



ABSTRACTS

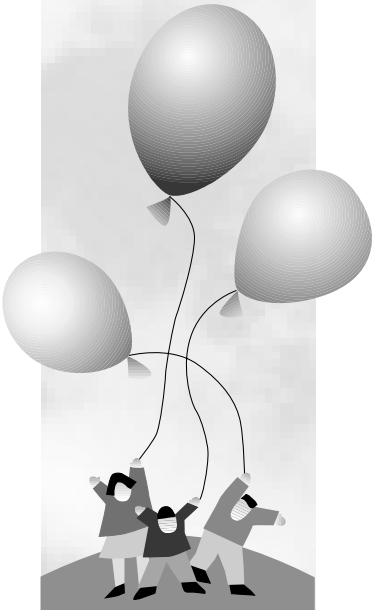
Monday, May 1, 2000
2:45 p.m.

THE LUNG

Impacts of the Criteria Air Pollutants on the Developing Lung

John Balmes, M.D., University of California, San Francisco

- Children are probably at greater risk of respiratory tract injury due to ambient air pollutants than healthy adults because of both increased exposure and increased susceptibility of the developing lung.
- Children have a greater minute ventilation relative to body surface area at rest. They tend to spend more time and be more active outdoors. Their increased activity means that they increase their minute ventilation and breathe more through their mouths (leading to decreased nasal filtration). All of these factors contribute to an increased effective dose of an ambient pollutant for children active outdoors relative to the typical adult.
- Children may have a greater susceptibility to pollutant-induced respiratory tract injury because repair mechanisms may retard lung growth at maturation. There is limited epidemiological evidence that exposure to ozone during childhood, especially during infancy, may affect adult lung function (decreased flow at low lung volumes). There is stronger evidence from the longitudinal USC-CARB Children's Health Study that exposure to oxides of nitrogen and particulate matter is associated with reduced rates of growth in spirometrically measured lung function.
- There is considerable toxicological evidence that exposure to oxidant pollutants increases the susceptibility of experimental animals to both bacterial and viral infections. The strongest epidemiological evidence of a criteria pollutant-associated increased risk of respiratory infections is for indoor exposure to oxides of nitrogen.
- There is reasonably strong epidemiological evidence that risk of asthma exacerbations is associated with exposure to ozone, sulfur dioxide, and particulate matter. There is also corroborating controlled human exposure study data for ozone and sulfur dioxide. What is not known is whether the long-term course of childhood asthma is affected by recurrent pollutant-associated exacerbations. It is also not known whether there is a subgroup(s) of asthmatic children that is at increased risk of pollutant-associated effects nor what are the genetic and/or environmental determinants of risk.
- Pollutants capable of inducing oxidant injury (ozone, oxides of nitrogen, diesel exhaust particulate) appear to have an adjuvant effect on airway allergic responses.



ABSTRACTS

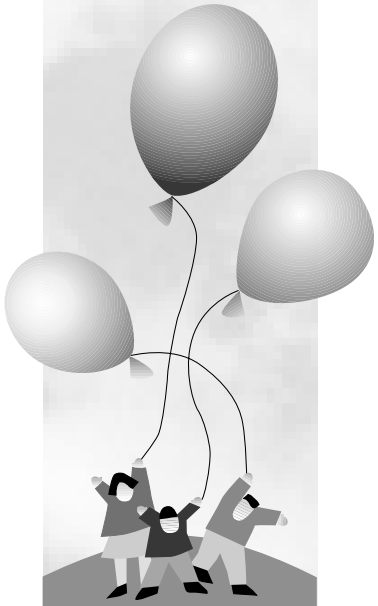
Monday, May 1, 2000
3:30 p.m.

THE LUNG

Possible Role of Hazardous Air Pollutants in Adverse Respiratory Responses among Children

George Leikauf, Ph.D., University of Cincinatti Medical Center

Previous epidemiological studies have linked air pollution with increased respiratory symptoms and exacerbation of asthma, especially among children. In the past, these studies have implicated specific criteria pollutants and environmental tobacco smoke. In addition, studies of children suggest that adverse health effects can occur at concentrations below those that produce effects in controlled animal and human exposures. The latter typically involve exposures to single pollutants, although recently studies with concentrated ambient particulate matter have been initiated in several laboratories. Critical to the interpretation of these results is knowledge of the physical and chemical properties of particulate matter that are responsible for the observed decrements in lung function. Several members of the 189 hazardous air pollutants listed in Title III: 1990 Clean Air Act Amendment can alter respiratory functions including airway reactivity. In July 1999, the USEPA further designated 33 compounds as posing the greatest health threat in urban areas. Of these compounds, several (including aldehydes: formaldehyde, acetaldehyde, and acrotein; and metals: nickel, chromium, and cadmium) have been associated with production of occupational asthma. Currently, little is known about personal exposure to these compounds among likely susceptible populations, such as children with asthma. In addition, emerging knowledge of genetic determinants of individual susceptibility may aid and focus future studies of gene-environmental interactions that impact children's health.



ABSTRACTS

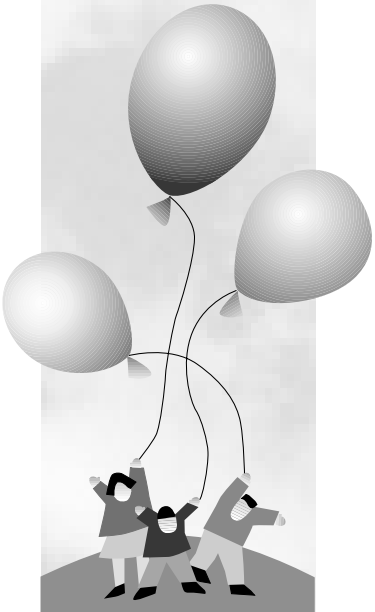
Tuesday, May 2, 2000
8:30 a.m.

ENDOCRINE FUNCTION

PCB's, DDT, Breastfeeding, and Growth in North Carolina Children Followed From Birth to Puberty

Walter Rogan, M.D., National Institute of Environmental Health Sciences

Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) are ubiquitous toxic environmental contaminants. One form of DDE is a weak estrogen. We followed a birth cohort of about 900 North Carolina children born between 1978 and 1983 and measured concentration of chemicals in breast milk fat and duration of lactation, which allowed us to estimate both pre- and post-natal dose to the child and the concentration in the mother. Mothers with higher DDE levels weaned earlier, perhaps because the DDE inhibited the action of prolactin on the breast. Follow-up of 594 children through puberty showed that height of boys at puberty increased with transplacental exposure to DDE, as did weight adjusted for height; adjusted means for those with the highest exposures were 6.3 cm and 6.9 kg larger than those with the lowest. There was no effect on the ages at which pubertal stages were attained. Lactational exposures to DDE had no apparent effects; neither did transplacental or lactational exposure to PCBs. Girls with the highest transplacental PCB exposures were heavier for their heights than other girls by 5.4 kg, but differences were significant only if the analysis was restricted to whites. We conclude that endocrine related phenomena, such as duration of lactation and body size at puberty, are affected by background levels of exposure to these chemicals.



ABSTRACTS

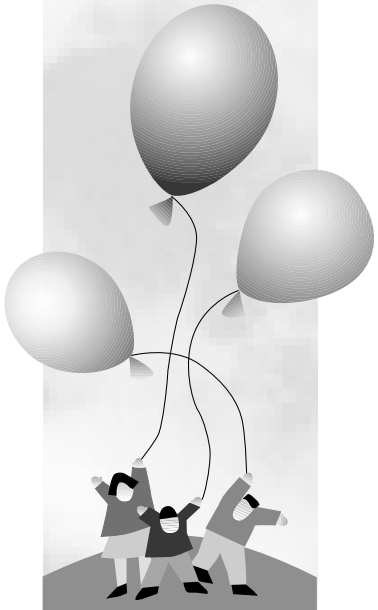
Tuesday, May 2, 2000
9:20 a.m.

IMMUNOTOXICITY AND SENSITIZATION

Development and Maturation of the Immune System: Vulnerability to Toxicants

Steven Holladay, Ph.D., Virginia Polytechnic University

Fetal and early postnatal life represent critical periods in vertebrate immune system development. Disruption of such development by perinatal immunotoxic chemical exposure has been widely described in experimental animal models. Resultant inhibited postnatal immune responses in such animals are often more dramatic and persistent than following exposure during adult life. Further, recent reports suggest that prenatal exposure to immunotoxicants may exacerbate postnatal aberrant immune responses (e.g., hypersensitivity disorders; autoimmune disease) in genetically predisposed rodents. Very limited information is available regarding the possibility of inhibited postnatal immune capacity in humans as a result of developmental immunotoxicant exposure. The multifactorial nature of hypersensitivity and autoimmune responses will further complicate elucidation of possible relationships between chemical exposure during ontogeny of the human immune system and immune-related disease later in life. Taken together, however, the available animal data suggest the potential for altered postnatal immune function in humans exposed to immunotoxicants (e.g., environmental chemicals; therapeutic agents) during fetal and/or early post-natal life.



ABSTRACTS

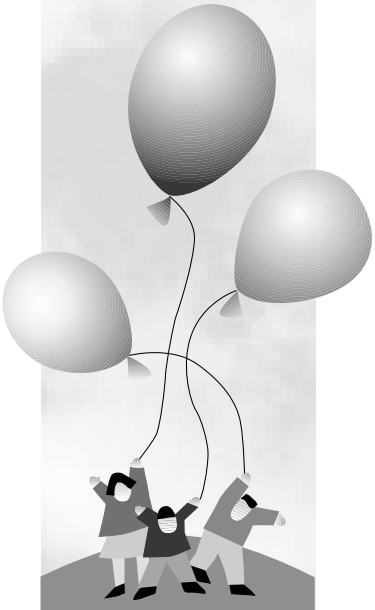
Tuesday, May 2, 2000
10:20 a.m.

IMMUNOTOXICITY AND SENSITIZATION

Developmental Immunology and Potential Windows of Vulnerability to Asthma

John Armstrong, Ph.D., Immuarm, Inc.

The scope of this talk will be to take the known effects of specific environmental toxins and mesh them within timelines of human immunological development for presentation as potential windows of vulnerability to the initiation of asthma. Aspects of the cellular, humoral, and innate immune responses to allergens and other factors involved in asthma induction will be presented, and toxicant-mediated skewing of T_H1 and T_H2 cellular responses *in utero*, in the neonatal period, and in early childhood will be discussed. Data from animal studies will be included for consideration in support of the projected potential susceptibility periods. In addition to contemporary beliefs and trends in the field of children's asthma, some findings from the draft of an IMMUNARM monograph recently submitted to the USEPA entitled *"An Assessment of the State of the Science on Acquired Immunity and Immunotoxicity in Development and Children's Health Protection*" will be presented with permission from the EPA's Office of Children's Health Protection.



ABSTRACTS

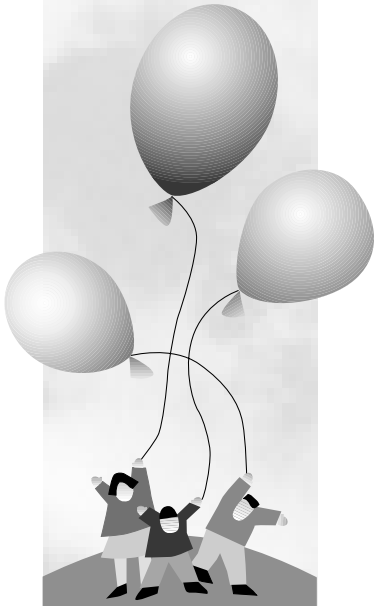
Tuesday, May 2, 2000
11:00 a.m.

CARCINOGENICITY

Re-evaluating Cancer Risk Estimates for Short-term Exposure Scenarios

Chris Portier, Ph.D., National Institute of Environmental Health Sciences

Estimates of cancer risk from short-term exposure to carcinogens generally rely on cancer potency values derived from chronic, lifetime exposure studies and assume that exposures of limited duration are associated with a proportional reduction in cancer risk. The validity of this approach was tested empirically using data from chronic lifetime and stop-exposure studies of carcinogens conducted by the National Toxicology Program. Eleven compounds were identified as having data sufficient for comparison of relative cancer potencies from short-term versus lifetime exposure. The data were modeled using the chronic data alone, and also using the chronic and the stop-exposure data combined, where stop-exposure doses were adjusted to average lifetime exposure. Maximum likelihood estimates of the dose corresponding to a 1% added cancer risk ED01 were calculated along with their associated 95% upper and lower confidence bounds. Statistical methods were used to evaluate the degree to which adjusted stop-exposures produced risks equal to those estimated from the chronic exposures. For most chemical/cancer endpoint combinations, inclusion of stop-exposure data reduced the ED01, indicating that the chemical had greater apparent potency under stop-exposure conditions. For most chemicals and endpoints, consistency in potency between continuous and stop-exposure studies was achieved when the stop-exposure doses were averaged over periods of less than a lifetime in some cases as short as the exposure duration itself. These observations suggest that the typical linear adjustments for less than a lifetime exposure in cancer risk assessment on average will underestimate the risks resulting from short-term exposures to some carcinogens.



ABSTRACTS

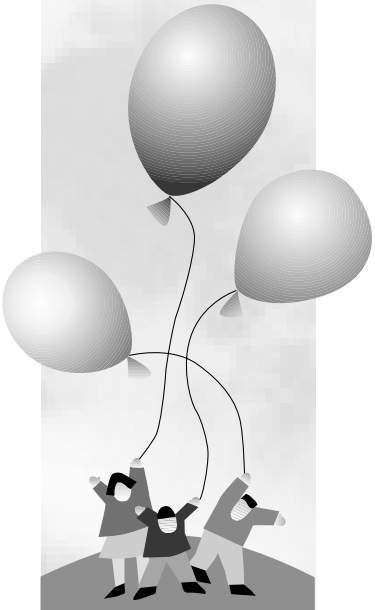
Tuesday, May 2, 2000
1:00 p.m.

CARCINOGENICITY

Characteristics of Risk of Perinatal Carcinogenesis

Lucy Anderson, Ph.D., D.A.B.T, National Cancer Institute

Many models are used in two general ways in the context of perinatal carcinogenesis: (1) to test specific chemicals as potential perinatal carcinogens, and (2) to characterize the perinatal carcinogenesis process, with regard to mechanisms, susceptibility factors, and modulatory effects. Phenomena which are found to pertain to several animal species may well be meaningful for the human. Such findings may help in the design or interpretation of human clinical and epidemiological studies. Perinatal carcinogenesis includes three distinct time periods of exposure: preconceptional, transplacental, and neonatal/infant. Preconceptional carcinogenesis probably involves a novel mechanism, which, when established for an animal model, may fruitfully be pursued in humans. This problem will be discussed. For transplacental and neonatal exposures, a number of generalizations can be made, based on a fairly large body of literature. (1) Any chemical which is carcinogenic in adults, is likely to be carcinogenic in fetuses and newborns. (2) The relative effect may be greater or less than in adults, depending on a variety of factors, which include numbers of cells at risk, rate of cell division, differentiation characteristics such as ability to activate or detoxify chemicals, DNA repair capacity, protective effects of maternal metabolism, etc. Examples will be given. (3) Modulation of some of these factors, by genetics or chemical treatment, can enhance or decrease tumor initiation. (4) Initiation of tumors in rodent fetuses and newborns involves genotoxic damage, non-genotoxic adult carcinogens that require chronic exposure to be effective, are not perinatal carcinogens. (5) The types of tumors initiated are characteristic of the species and strain primarily. (6) The tumors are generally of adult type, and may not appear until the old age of the animal. However, among these are counterparts of several of the more common childhood cancers, Wilms' tumor of kidney, sarcomas, and leukemia. (7) Perinatal exposures may increase responsiveness to carcinogen exposures later in life. The only perinatal carcinogen for which there are sufficient data to compare animal and human responses is diethylstilbestrol. This comparison will be presented. There are large gaps in the animal model data base, in particular, study of most of the suspected susceptibility factors in more than one species, systematic investigation of many human-exposure chemicals, and side-by-side comparisons of molecular changes in animal and human tumors. Furthermore the availability of genetically engineered animals now makes it possible to test hypotheses directly. Unfortunately, study of perinatal carcinogenesis in animal models is not currently an active area.



ABSTRACTS

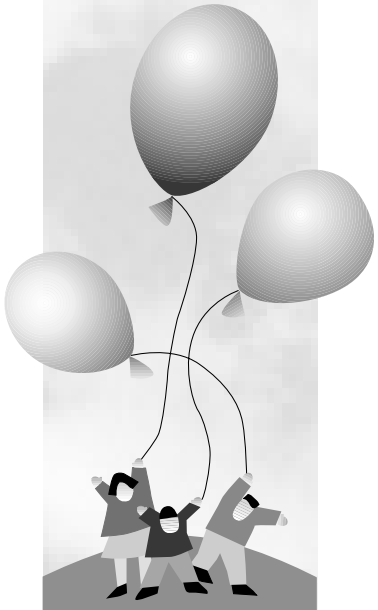
Tuesday, May 2, 2000
2:00 p.m.

PHARMACOKINETIC ISSUES

Pharmacokinetic Parameters

Dale Hattis, Ph.D., Clark University

The pharmaceutical literature contains substantial amounts of information on the pharmacokinetics of various drugs in children of various ages and adults. This presentation is a snapshot of our ongoing comparative analyses of these data. The work asks two basic questions: (1) For a variety of specific parameters that are easily related to the pharmacokinetic components of susceptibility to adverse effects (clearance rates, whole body elimination half-lives, steady state volume of distribution, maximal blood concentrations after dosing, and integrated "Area Under the Curve" of concentration X time), how often are the mean values of the parameters seen in children of various ages different from adult means by various amounts in specific directions suggestive of increased or decreased risk? (2) For the same specific parameters and age groups, is the interindividual variability seen in children different from the variability seen in adults (if so, how often is the variability greater or less, and by how much?). The early impression from the analyses we have done so far is that the most conspicuous differences in both these areas are seen for the neonatal period. As we proceed we will draw inferences for expected distributions of the pharmacokinetic portions of individual variability in susceptibility for otherwise untested environmental chemicals. A companion presentation (by Gary Ginsberg) will explore differences in distributions of child/adult pharmacokinetic parameter values segregated by mechanistic categories (e.g. elimination via different pathways and metabolism by various P450's, glucuronidation, and other enzyme systems).



ABSTRACTS

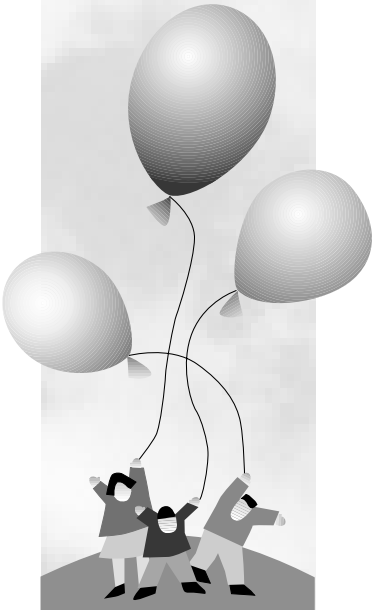
Tuesday, May 2, 2000
2:50 p.m.

PHARMACOKINETIC ISSUES

Exposure to Dose Models: Their Uses in Helping Access Relevant Dose in Children

Jerry Blancato, Ph.D., U.S. Environmental Protection Agency

Many different factors influence the risk in the myriad of human sub-populations. Children might be at either greater or lesser risk because of unique factors associated with their age, size, vulnerability, resistance or exposure conditions. For example, because of more rapid cell turnover and generally healthier cardiovascular systems, children may be at less risk from infections resulting from poor wound healing. Factors that impact risk can, for simplicity, be grouped into two main categories. First, there are biological considerations. Immunocompetency, respiratory maturity, tissue vulnerability, enzymatic development and activity are all examples. Second, there may be special exposure conditions and activities. Frequency, duration and location of contact with pollutants may be very different for children. Behaviors such as mouthing, dietary preferences, beverage consumption, times spent at special locations are examples of some of these exposure considerations. Exposure-to-dose models can be used to help account for some of these considerations. These models, as described here, are centered around physiologically based pharmacokinetic (PBPK) models. PBPK models characterize the time-course disposition of xenobiotics and their biotransformation products within the body. These models are based on knowledge of anatomy and physiology. While not designed to account for differences in vulnerability, sensitivity, or response rates, they account for differences in blood flows, body and organ size, tissue composition, clearance, and metabolic rates and pathways. With specific knowledge about physiologic and metabolic processes the models are used to address the impacts of age-related differences on relevant internal doses. Specific exposure input modules can be designed and combined with the PBPK models. The resultant exposure-to-dose models describe and quantify the toxicologically relevant dose resulting from simulated exposure conditions. Exposure input modules can also include those that take actual time-course exposure concentration data. Sensitivity and variation modules are added so as to better characterize populations of interest rather than just a single individual. The USEPA is developing an architecture, the Dose Estimating Exposure Model (DEEM). DEEM is used to specifically estimate various measures of toxicologically relevant doses from simulating exposure scenarios or from actual monitored exposure histories. This presentation will discuss how such models can be used to estimate the impact of various physiological and exposure parameters and conditions on relevant doses. Much insight about the impact of physiology and exposure conditions of children can be revealed by using these types of model systems.



ABSTRACTS

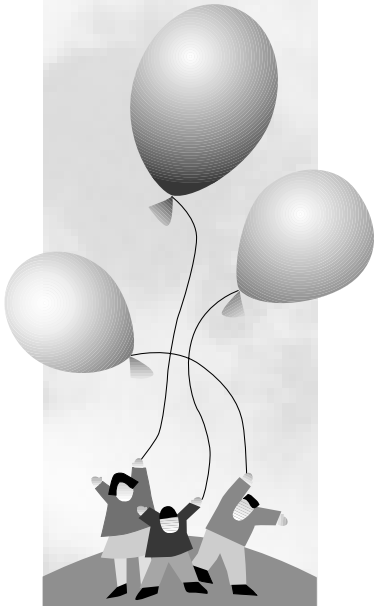
Tuesday, May 2, 2000
3:20 p.m.

PHARMACOKINETIC ISSUES

Xenobiotic Metabolism and Chemical Fate from Early Childhood Onward

Gary Ginsberg, Ph.D., Connecticut Department of Public Health

Development of xenobiotic clearance pathways begins prenatally but in many cases is quite immature in human neonates. This appears to be true for a variety of key metabolic enzymes including certain hepatic mixed function oxidases involved in activation of chemicals to toxic species (Cyp 2E1, Cyp 1A2). These activating Cyp isozymes reach and can surpass adult activities within the first years of life, suggesting xenobiotic activation via the Cyp 2E1 and 1A2 pathways (e.g., benzene, chlorinated solvents, polycyclic aromatic hydrocarbons) are greater after one year of age than in neonates and possibly also in adults. However, other Phase I enzymes (other Cyps) as well as Phase II enzymes (especially glucuronidation) and renal clearance are also not well developed in the neonate. We have developed a database describing the human pharmacokinetics (half-life, clearance, volume of distribution, peak concentration, blood AUC) of a broad array of therapeutic drugs across various age groups. This is more fully described in the companion presentation by Dale Hattis. In many cases, the drugs in this database are substrates for specific clearance pathways and so can be used to probe the development of these pathways. Our presentation will provide an indication of how large the inter-age group differences are with respect to key activation and removal pathways, and the degree of variability seen in young children in the compiled datasets. This analysis will improve our understanding of how a pharmacokinetic uncertainty factor is necessary in adult-based risk assessments to ensure protection of early life stages on dosimetry grounds. The quantitative comparisons for specific pathways may also be used, in combination with age-specific physiologic parameters (body size, lipid and water volume, tissue compartment volumes, blood flows, serum protein levels), to develop age-specific physiologically-based pharmacokinetic (PBPK) models. These models hold the potential to refine children's risk assessments by simulating how the balance between metabolic activation and detoxification/clearance shifts during human development.



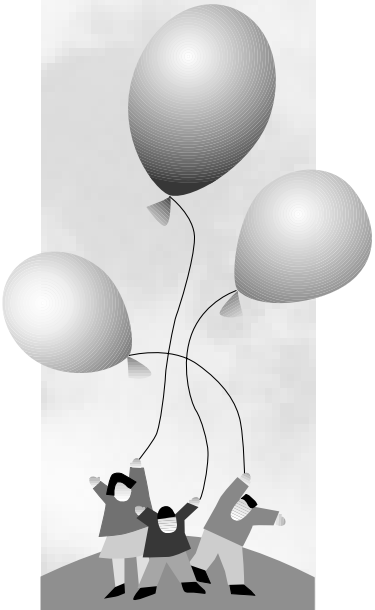
PRESENTERS

Lucy Anderson, Ph.D., D.A.B.T.
Chief, Cellular Pathogenesis Section
Laboratory of Comparative Carcinogenesis
National Cancer Institute

With a Ph.D. in Developmental Biology, and both undergraduate and postdoctoral training in biochemistry, Dr. Lucy Anderson has been investigating the mechanisms of perinatal carcinogenesis in animal models for more than twenty years. Of a total bibliography of 150 papers, she has approximately sixty primary publications and five review/overview articles on this topic. Currently, Dr. Anderson is Chief of the Cellular Pathogenesis Section of the Laboratory of Comparative Carcinogenesis, at the National Cancer Institute (NCI). She has participated in numerous national and international symposia and workshops on perinatal carcinogenesis and frequently lectures on the topic. Current research work in progress includes a study of DNA adducts from NNK or the environmental carcinogen N-nitrosodimethylamine delivered translactationally, and the effects of ethanol on these adduct levels; analysis of mutations in the K-ras oncogene in lung tumors following transplacental exposure to AZT or preconceptional exposure to chromium (iii) chloride; and investigation of the mechanism of preconceptional carcinogenesis by chromium (III) chloride by use of microarray analysis of gene expression in tissues of the offspring.

John Armstrong, Ph.D.
President, Immunarm, Inc.

Dr. John Armstrong is the President of Immunarm, Inc., a company incorporated in 1998 to provide research and education services in the field of immunology. Dr. Armstrong earned his Ph.D. in Immunology in 1996 in the Cancer Immunobiology Center (CIC) laboratory of Dr. Ellen Vitetta at the University of Texas, Southwestern Medical Center in Dallas. His dissertation research included the synthesis and pre-clinical testing of tumor-specific immunotoxins and bi-specific antibodies. He then gained strong, industrial laboratory experience in the human physiologic response to toxicants and xenobiotics in the Drug Metabolism and Pharmacokinetics (DMPK) Department of Sandoz Pharmaceutical Company in Basel, Switzerland, where he studied the biotransformation of experimental compounds by enzymes in the liver, gut and kidneys using animal and human tissue slices. Further post-doctoral training was acquired in the Biochemistry and Pharmacology Section of the Laboratory of Immunology at the National Institute of Health in Bethesda, Maryland. During this time, Dr. Armstrong elucidated certain complexities of biochemical signal transduction networks involved in T cell signaling and their effects on immune activation and suppression. He has co-authored one book chapter and is the first

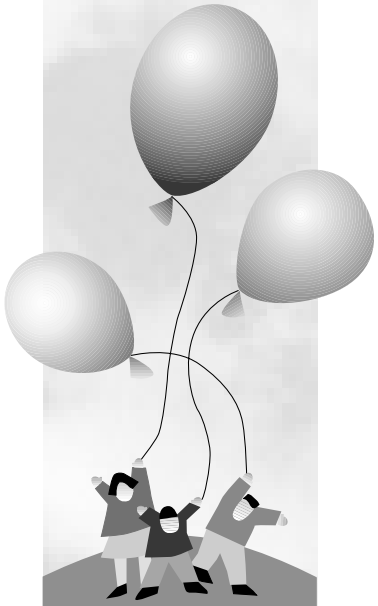


PRESENTERS

author or co-author of at least five other manuscripts published, submitted or in preparation from this laboratory. Dr. Armstrong has also served as a Senior Scientist for the KEVRIC Company, where he managed a project for the National Cancer Institute (NCI) involving database management of all cancer studies supported by the NCI. Upon formation of Immunarm, Inc., he was awarded a contract by the U.S. EPA's Office of Children's Health Protection (OCHP) to write a 500 page monograph as *"An Assessment of the State of the Science on Acquired Immunity and Immunotoxicity in Development and Children's Health Protection."* Dr. Armstrong continues to co-teach the Principles of Immunology at the University of Maryland in College Park.

John Balmes, M.D.
University of California, San Francisco

Dr. John R. Balmes is a Professor of Medicine at the University of California, San Francisco (UCSF) where he is the Chief of the Division of Occupational and Environmental Medicine at San Francisco General Hospital (SFGH), and an Attending Physician in Pulmonary/Critical Care Medicine at SFGH. Dr. Balmes is board-certified in internal medicine and pulmonary medicine and has additional fellowship training in occupational medicine. Dr. Balmes leads an active research program involving controlled human exposure studies of the respiratory effects of ambient air pollutants in his Human Exposure Laboratory at the UCSF Lung Biology Center. His laboratory currently is studying the acute inflammatory effects of multi-day exposure to ozone in subjects with asthma, the acute inflammatory and lung function effects of exposure to smoke from burning vegetative matter such as rice straw, and whether there are differences in the acute inflammatory and lung function responses of young adults from Los Angeles as compared to young adults from the SF Bay Area. Dr. Balmes has assisted the federal EPA in the preparation of several criteria documents (Nitrogen Oxides, Ozone, and Particulate Matter), is a member of the Cal/EPA Air Quality Advisory Committee, and is a member of the Research Screening Committee of the California Air Resources Board. He has long been active in the American Thoracic Society and American Lung Association and recently received the Clean Air Award from the American Lung Association of California.



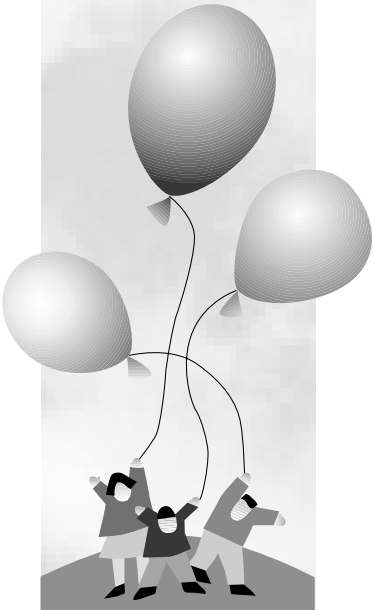
PRESENTERS

Stanley Barone, Jr., Ph.D.
Research Biologist, Neurotoxicology Division
U.S. Environmental Protection Agency

Dr. Stanley Barone is a Research Biologist in the Neurotoxicology Division at the U.S. Environmental Protection Agency (EPA). His research program is focused on issues of susceptibility of the developing nervous system to neurotoxicants. He joined the EPA in 1990 under a contract position and has worked in the Cellular and Molecular Branch at EPA. Dr. Barone's publications include investigations of the age-related neurotoxicity of organometals, triethyltin and trimethyltin and the latent neurotoxicity of metals, includes examination of the effects methlylmercury on neurotrophin as it relates to adverse consequences on neural growth and differentiation of the brain. More recently, Dr. Barone's research has focused primarily on qualitative and quantitative differences that result from developmental exposure to cholinesterase inhibiting pesticides on the development of the nervous system. His work aims to provide for improvement of test methods and derivation of predictive models for developmental neurotoxicants.

Jerry N. Blancato, Ph.D.
Chief, Human Exposure Research Branch
U.S. Environmental Protection Agency

Dr. Jerry N. Blancato is Chief of the Human Exposure Research Branch at the U.S. Environmental Protection Agency (EPA). His research interests include the development of techniques for application of physiologically-based pharmacokinetic modeling in exposure and risk assessments. Specific aims of his work are to find better ways to quantitatively compare relevant dose after different exposure scenarios and different physiologic profiles. He has authored numerous presentations, papers, and book chapters on the subject of dose estimation. Prior to 1989, Dr. Blancato worked at the EPA's National Center for Environmental Risk where he worked on several risk assessments, most notably the update for methylene chloride. Since 1989, he has been the Principal Investigator of the National Exposure Research Laboratory's exposure-to-dose modeling program. In addition, Dr. Blancato teaches a course in Pathophysiology at the Community College of Southern Nevada where he is an Adjunct Faculty. He is also an Associate Faculty Member at the University of Nevada, Las Vegas where he serves on several graduate advisory committees. Dr. Blancato received a Bachelors degree in Chemistry from Fordham University, a Masters degree in Experimental Pathology from Hahnemann Medical College and Hospital, and a Ph.D. in Applied Sciences/Biomedical Engineering from the University of Delaware.



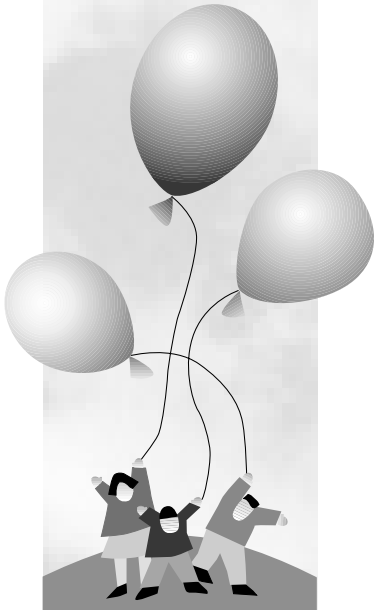
PRESENTERS

Delia A. Dempsey, M.D.
Assistant Professor, Pediatrics, Medicine and Clinical Pharmacology
University of California, San Francisco

Dr. Delia A. Dempsey is a Pediatrician based at San Francisco General Hospital, and an Assistant Professor in Pediatrics, Medicine and Clinical Pharmacology, at the University of California, San Francisco. In addition, she is an Attending Physician for the California Poison Control System, and for the Pediatric Environmental Health Specialty Unit. Dr. Dempsey graduated from the University of California, San Francisco, where she also received her pediatric training, was a Pediatric Chief Resident, and completed her fellowship in Clinical Pharmacology and Toxicology. Her research interest has been developmental pharmacology. She has also investigated the pharmacokinetics and clinical effects of cocaine and nicotine in the newborn, and the metabolism of nicotine in pregnant women.

Brenda Eskenazi, Ph.D., M.A.,
Professor, Maternal and Child Health and Epidemiology
Chair, Maternal and Child Health
University of California, Berkeley, School of Public Health

Dr. Brenda Eskenazi, Ph.D., Professor of Maternal and Child Health and Epidemiology and Chair of Maternal and Child Health at U.C. Berkeley's School of Public Health, has studied the effects of environmental and occupational exposures to reproductive, perinatal and children's health for two decades. She has conducted research on the reproductive and developmental effects of passive and active exposure to cigarette smoke and exposure to caffeine, solvents and dioxins. She has also studied the reproductive health risks to women employed by the semiconductor industry and the maquiladora industry near the U.S. Mexico border, and also men employed in the dry cleaning industry. Dr Eskenazi is the director of the U.C. Berkeley Center for Children's Environmental Health Research and CHAMACOS, a community-university partnership that brings together researchers, farm workers, growers, community groups, medical providers, and others committed to understanding the potential effects of pesticide and other exposures to children.



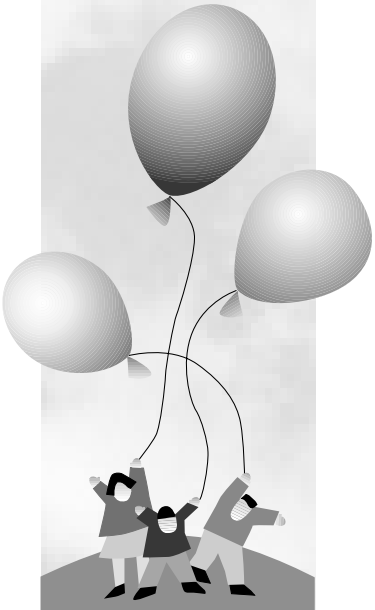
PRESENTERS

Elaine Faustman, Ph.D.
University of Washington

Elaine M. Faustman, Ph.D., received her Bachelors degree in Chemistry and Zoology from Hope College (1976) and her Doctorate in Pharmacology/Toxicology from Michigan State University (1980). She took her postdoctoral training in Toxicology and Environmental Pathology at the School of Medicine, University of Washington. Dr. Faustman is currently Professor and Director at the Institute for Risk Analysis and Risk Communication at the School of Public Health and Community Medicine, University of Washington where she has received the Outstanding Teaching Award. Her research interests include quantitative risk assessment for non-cancer endpoints, reproductive and developmental toxicology of metals and in vitro and molecular biological methodologies. Dr. Faustman is the Principle Investigator of a newly funded EPA-NIEHS Child Health Center, which is currently evaluating key mechanisms defining the children's susceptibility to pesticides. She is an Elected Fellow of the American Association for the Advancement of Science and is currently serving as Chair for the National Academy of Sciences Committee on Developmental Toxicology and as a member for the NIEHS-NTP Committee on Alternative Toxicology Methods. Dr. Faustman has served on the NIEHS-NTP Board of Scientific Counselors and the National Academy of Sciences Committee in Toxicology. She has served as Associate Editor of Fundamental and Applied Toxicology and on editorial boards of Reproductive Toxicology and Toxicology Methods.

Michael Firestone, Ph.D.
Science Director, Office of Children's Health Protection
Environmental Protection Agency

Dr. Michael Firestone is the Science Director for EPA's Office of Children's Health Protection (OCHP). Prior to joining OCHP, he was a Science Advisor to the Assistant Administrator for the Office of Prevention, Pesticides and Toxic Substances (OPPTS), where he also played the role of Research Coordinator, and most recently, Acting Associate Director of the Office of Science Coordination and Policy within OPPTS. Among his agency-wide activities, Dr. Firestone chaired the team which developed EPA's policy on Probabilistic Modeling, co-authored a research strategy to support development of residential exposure testing and assessment guidelines focused on children as a potentially highly exposed group, and helped develop EPA's guidance related to the Cumulative Risk Assessment Planning and Scoping.



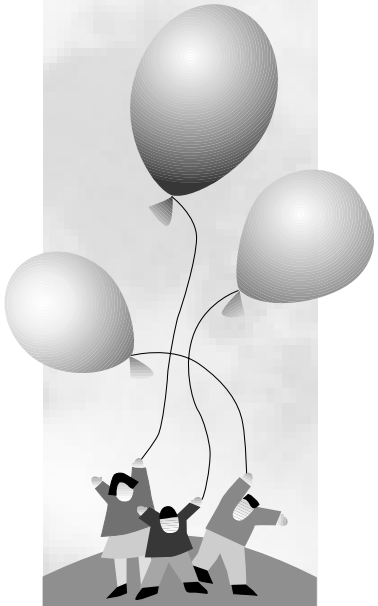
PRESENTERS

Gary L. Ginsberg, Ph.D.
Toxicologist, Connecticut Department of Public Health
Division of Environmental Epidemiology & Occupational Health

Dr. Gary L. Ginsberg is currently a Toxicologist at the Connecticut Department of Public Health, within the Division of Environmental Epidemiology and Occupational Health. He is responsible for human health risk assessments conducted in the state. He is also the Project Manager for a cooperative agreement with the Environmental Protection Agency which is researching pharmacokinetic differences between children and adults. Dr. Ginsberg serves as Adjunct Faculty at the Yale School of Medicine and the University of Connecticut School of Public Health where he is involved in several graduate courses. He received a Ph.D. in toxicology from the University of Connecticut and was a post-doctoral fellow in carcinogenesis/ mutagenesis at the Coriell Institute for Medical Research. Dr. Ginsberg's toxicology experience has involved a variety of settings, including basic research, teaching, and working within the pesticide and consulting industries, and now working in public health. He has published in the areas of toxicology, carcinogenesis, and physiologically-based pharmacokinetic modeling.

Lynn R. Goldman, M.D., M.P.H.
Adjunct Professor, Johns Hopkins University

Dr. Lynn Goldman, a Pediatrician and an Epidemiologist, is an Adjunct Professor at the Johns Hopkins University, School of Hygiene and Public Health. At Hopkins, she is Principal Investigator on Children's Health for the Pew Environmental Health Commission, which informs the public and policy makers about environmental health hazards that threaten the nation's health and recommends policies for protection and prevention. Until January 1999, she served at the Environmental Protection Agency as Assistant Administrator for the Office of Prevention, Pesticides and Toxic Substances (OPPTS). As a pediatrician trained in environmental sciences, public health, and preventive medicine, she has been a scientific and policy leader at both the state and national level. Dr. Goldman is widely recognized as one of the nation's foremost experts in children's health and the environment. Dr. Goldman received a Bachelors degree in Conservation of Natural Resources from the University of California, Berkeley, a Masters of Public Health degree from the Johns Hopkins University School of Public Health, and an M.D. from the University of California, San Francisco. She completed a pediatric residency at Children's Hospital, Oakland and a preventive medicine residency at the University of California, Berkeley, and is board certified in pediatrics.



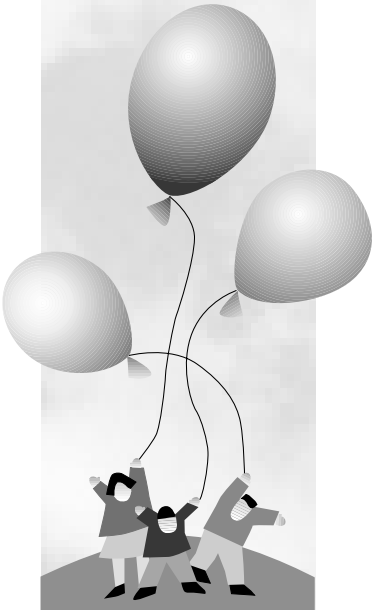
PRESENTERS

Mari Golub, Ph.D.
Staff Toxicologist
Office of Environmental Health Hazard Assessment

Dr. Mari Golub is a Staff Toxicologist at the Office of Environmental Health Hazard Assessment (OEHHA), and holds a position as Adjunct Professor at the University of California, Davis where she has conducted research over the past 20 years in the area of Developmental Toxicology. Most recently, she has initiated a EPA-sponsored study of endocrine disruption in adolescence, using the rhesus monkey as a model for the research. At OEHHA, Dr. Golub works in the Reproductive Toxicology Unit of the Reproductive and Cancer Hazard Assessment Section. Her review, "Adolescent Health and the Environment," was published in the April 2000 issue of *Environmental Health Perspectives*. Dr. Golub holds a Ph.D. from the University of Michigan and a Masters degree from the University of California, Davis. Additionally, she is certified by the American Board of Toxicology.

Dale Hattis, Ph.D.
Research Professor, Center for Technology, Environment and Development
George Perkins Marsh Institute, Clark University

Dr. Dale Hattis is Research Professor with the Center for Technology, Environment and Development (CENTED) of the George Perkins Marsh Institute at Clark University. For the past twenty-five years he has been engaged in the development and application of methodology to assess the health, ecological and economic impacts of regulatory actions. His work has focused on the development of methodology to incorporate interindividual variability data and quantitative mechanistic information into risk assessments for both cancer and non-cancer endpoints. Specific studies have included quantitative risk assessments for hearing disability in relation to noise exposure, renal effects of cadmium, reproductive effects of ethoxyethanol, neurological effects of methyl mercury and acrylamide, and chronic lung function impairment from coal dust, four pharmacokinetic-based risk assessments for carcinogens (for perchloroethylene, ethylene oxide, butadiene, and diesel particulates), an analysis of uncertainties in pharmacokinetic modeling for perchloroethylene and an analysis of differences among species in processes related to carcinogenesis. He is a Councilor of the Society for Risk Analysis, and serves on the editorial board of its journal, *Risk Analysis*. He holds a Ph.D. in Genetics from Stanford University and a Bachelors degree in Biochemistry from the University of California, Berkeley.



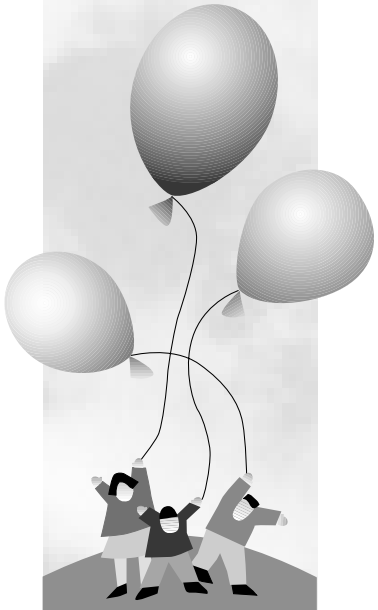
PRESENTERS

Steven D. Holladay, Ph.D.
Associate Professor, Virginian-Maryland Regional College of Veterinary Medicine

Dr. Steven Holladay is Associate Professor of Anatomy and Toxicology at the Virginian-Maryland Regional College of Veterinary Medicine. He received his Ph.D. in Toxicology from North Carolina State University in 1989. His postdoctoral research followed at the National Institute of Environmental Health Sciences (NIEHS) and was focused in developmental immunotoxicology. Dr. Holladay co-authored the Developmental Immunotoxicity chapter in the Developmental Toxicology textbook of the popular Target Organ Toxicology Series. He has published numerous related journal articles, including several invited reviews in the journal of the *NIEHS, Environmental Health Perspectives*.

George D. Leikauf, Ph.D.
Professor, Department of Environmental Health, Department of Molecular and Cellular Physiology, and Department of Medicine, University of Cincinatti Medical Center

Dr. George D. Leikauf, Ph.D., is currently a Professor in the Departments of Environmental Health, Molecular and Cellular Physiology, and Medicine, at the University of Cincinnati Medical Center. He is the recipient of numerous honors and awards, including a Graduate Fellow from the National Institute of Environmental Health Sciences, and a Postdoctoral Fellowship from the National Heart, Lung, and Blood Institute. He has served as Principal Investigator on various projects, including Pathogenetics of Particulate Matter (Health Effects Institute, 1998-2000), and Short-Term Research Training for Minority Students (NIEHS, 1995-2000). Dr. Leikauf holds a Ph.D. in Environmental Medicine, a Postdoctoral degree in Respiratory Cell Biology, and a Masters degree in Environmental Medicine.



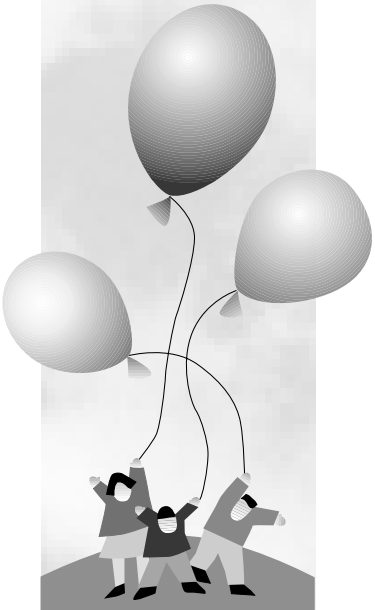
PRESENTERS

Kent Pinkerton, Ph.D.
Professor, School of Veterinary Medicine
University of California, Davis

Dr. Kent Pinkerton is a Professor of Anatomy, Physiology and Cell Biology in the School of Veterinary Medicine at the University of California, Davis. His research interests center on the respiratory system and health effects of airborne air pollutants during perinatal development. He has an active research program to study the health effects of exposure to environmental tobacco smoke during critical windows of lung development. He also is studying the effects of airborne particulate matter on the lungs of adult and aged rodents, with a special emphasis on complex mixtures of particles and gases. Dr. Pinkerton holds both a Ph.D. and a Masters degree from Duke University.

Christopher J. Portier, Ph.D.
Laboratory Chief, Laboratory of Computational Biology and Risk Analysis
Associate Director, Environmental Toxicology Program
National Institute of Environmental Health Sciences

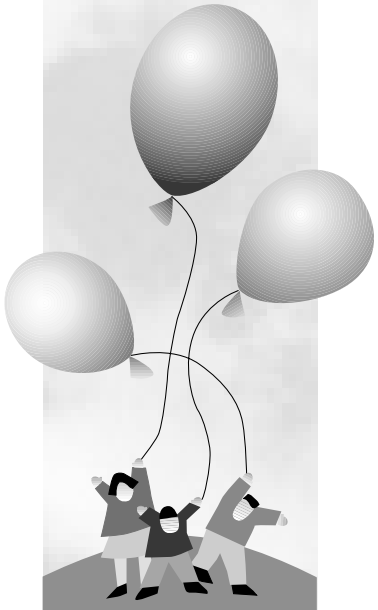
Dr. Christopher Portier currently serves as Laboratory Chief in the Laboratory of Computational Biology and Risk Analysis, and as Associate Director of the Environmental Toxicology Program at the National Institute of Environmental Health Sciences. His fields of research interest include Survival Analysis, Cancer Modeling, Environmental Risk Assessment, Computer Science, Toxicokinetics, and Theoretical Biology. He is the author of over 100 peer-reviewed publications in statistics, risk assessment, and cancer research. Dr. Portier holds both a Ph.D. and a Masters degree in Biostatistics from the University of North Carolina, Chapel Hill.



PRESENTERS

Deborah Rice, Ph.D.
Risk Assessor, National Center for Environmental Assessment
Environmental Protection Agency

Dr. Deborah Rice is currently a Risk Assessor in the area of neurotoxicology with the National Center for Environmental Assessment at the EPA. She received her Ph.D. in Toxicology from the University of Rochester. Dr. Rice previously was a Research Scientist in the Toxicology Research Division of Health Canada, where she headed a behavioral toxicology laboratory utilizing a large colony of macaque monkeys. Her research program focused on characterizing nervous system impairment produced by developmental exposure to the major environmental pollutants of lead, methylmercury, and PCBs. Dr. Rice identified impairment in visual, auditory, and somatosensory function as a result of early exposure, as well as an age-exposure interaction in functional decrement in aging monkeys. In addition, she identified behavioral deficits in monkeys exposed postnatally to an environmentally-relevant congener mixture of PCBs, and had blood PCB concentrations typical of environmentally-exposed humans. Dr. Rice is currently an Associated Editor for the journals *Neurotoxicology*, *Neurotoxicology and Teratology*, and *Environmental Research*. She has authored or co-authored over 100 research articles and book chapters in the areas of neurotoxic effects of specific agents, methodological approaches for neurotoxicology research and risk assessment.



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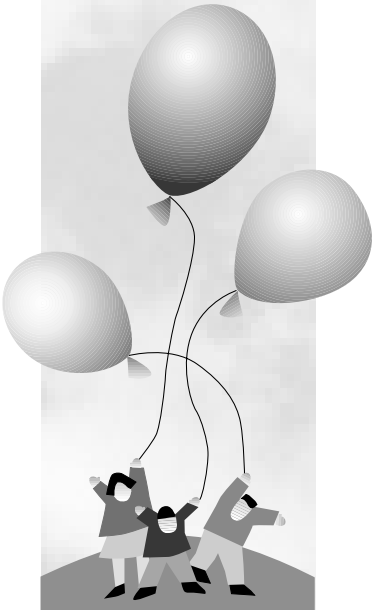
Walter J. Rogan, M.D.
National Institute of Environmental Health Sciences

Walter J. Rogan received an M.D. from the University of California, San Francisco, and a Masters degree in Public Health in Biostatistics from the University of California, Berkeley. After internship at San Francisco General Hospital, he came to National Institute of Environmental Health Sciences (NIEHS) in 1976. He has held a variety of positions there, including Chief of Epidemiology and Acting Clinical Director in the Division of Intramural Research. He has now returned to full-time research in the Epidemiology Branch. Dr. Rogan's research concerns the effect of pollutant chemicals on the growth and development of children. In a cohort study of North Carolina children exposed to background levels of PCBs and DDT, Dr. Rogan and his Co-Investigator Beth Gladen showed that transplacental but not lactational exposure to PCBs produced small but persistent delays in motor development detectable from birth to age two years. Studies also showed that DDE at higher levels was associated with markedly earlier weaning, replicated that finding in Mexico, and speculated that this might be because DDE is a weak estrogen. Dr. Rogan and his colleagues also studied a complex food poisoning episode in Taiwan, in which children were exposed transplacentally to PCBs and PCDFs. Dr. Rogan is now Project Officer for a four-site, randomized, controlled clinical trial of oral chelation therapy to prevent lead-induced disorders of growth, behavior and cognitive development in toddlers.

Ira B. Tager, M.D., M.P.H.
Professor of Epidemiology
University of California, Berkeley, School of Public Health

Dr. Ira B. Tager has had a longstanding research interest in the role of early life environmental exposures as risk factors for the development of childhood and adult obstructive long diseases (asthma, COPD). Many of his studies, dating back almost 20 years, have focused on the role of maternal pre-and post-natal cigarette smoking on the development of lung function during infancy, childhood and adolescence. These studies also included investigation of the relationship of levels of lung function in childhood to subsequent development of chronic respiratory symptoms and bronchial reactivity in adolescents. Approximately, seven years ago, Dr. Tager extended these interests to studies of the effects of lifetime exposures to ambient ozone concentrations on measures of small airway function in the late teen years and, most recently, to studies of the effects of ambient air pollution of lung function growth and disease progression in young children with asthma.



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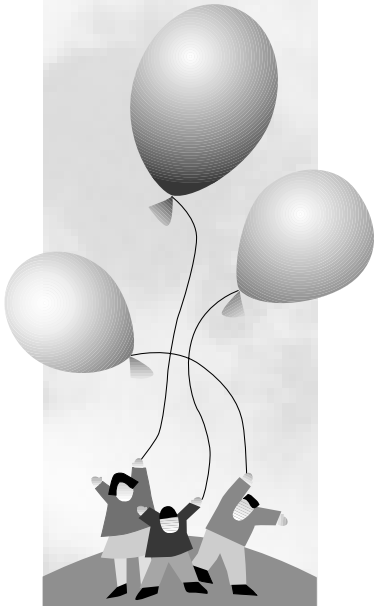

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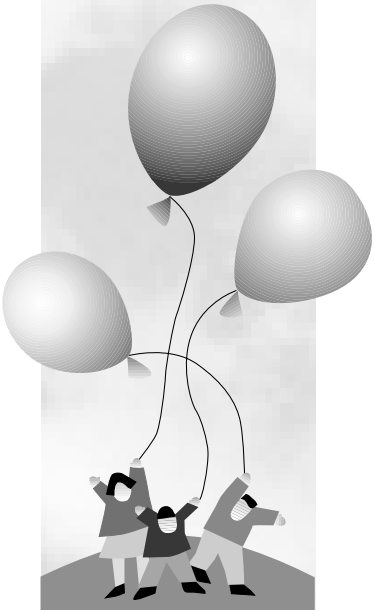

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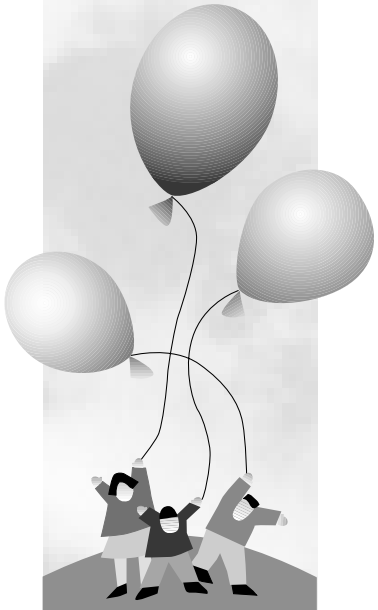

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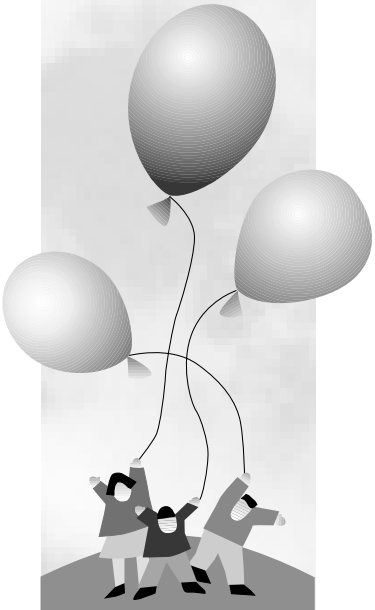

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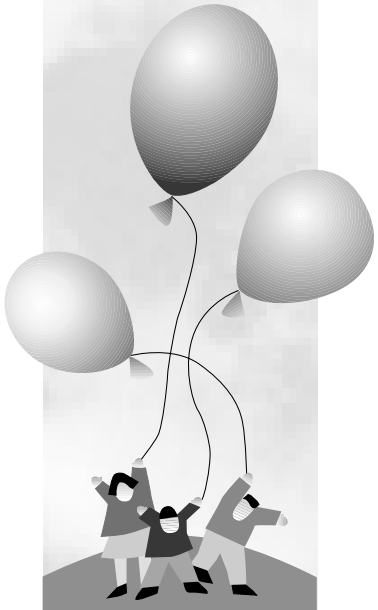

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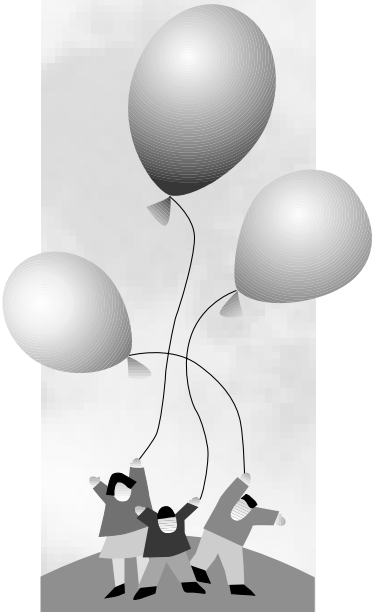

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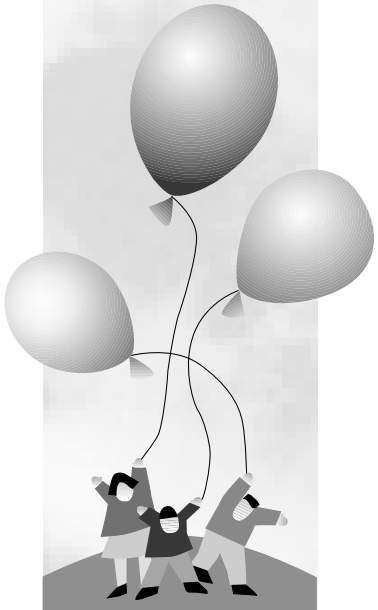

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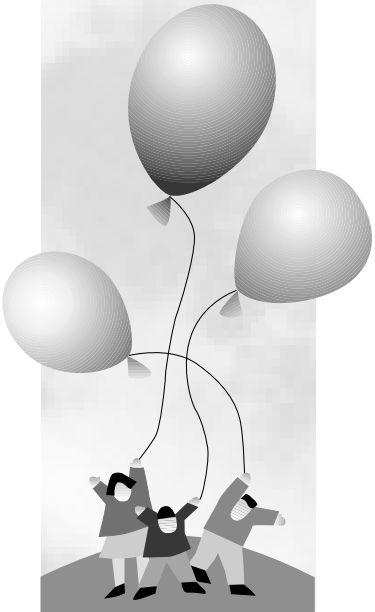

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